Merkel cell carcinoma (MCC) is an aggressive and rare cutaneous cancer with poor survival outcomes. We report here 2 cases of metastatic MCC (mMCC) for which a combination of avelumab, an anti-programmed death-ligand 1 (PD-L1) inhibitor, and radiotherapy (RT) was effective. In both cases, metastatic lesions outside the irradiated area decreased in size and eventually disappeared, and an abscopal effect was obtained. We believe that a combination of RT and immune checkpoint inhibitor (ICI) administration should be actively considered for treatment of mMCC.

**CASE REPORTS**

**Case 1.** A 70-year-old woman presented with a 1-month history of a red tumour on her right upper eyelid. Clinical examination revealed a 26-mm red-coloured hard mass (Fig. 1a), and an excisional biopsy revealed MCC. Therefore, wide local excision and biopsy of a sentinel lymph node (SLN) in the right side of the neck were performed. As the SLN was positive for metastasis, right cervical lymph node (LN) dissection and adjuvant RT (upper right eyelid: 50 Gy; right side of the neck: 60 Gy) were performed. Six months later, however, the patient developed subcutaneous metastasis in the right side of the neck (Fig. 1b) and LN metastasis in the right parotid gland (Fig. 1c). Subsequently she underwent RT (20 Gy) for the LN metastasis, and avelumab (10 mg/kg) was administered intravenously every 2 weeks. Eight weeks after the start of avelumab administration, the subcutaneous metastasis in the right cervical region, which had not been irradiated, gradually decreased in size and eventually disappeared (Fig. 1d). Computed tomography (CT) confirmed ablation of the metastatic LN (Fig. 1e). To date, avelumab has been continued. Within 24 h after the first administration, the patient developed a fever, which persisted until the time of the second administration; however, there was no fever after the third administration.

**Case 2.** An 86-year-old woman presented with a 1-month history of a red tumour on her nose. Clinical examination revealed a 10-mm red-coloured hard mass, and surgical excision was performed. An excisional biopsy revealed MCC. The patient was unwilling to undergo wide local excision. Fourteen months after the excisional biopsy, left cheek and bilateral LN metastases developed. The metastases to the left cheek and left cervical LN resulted in a large 50-mm subcutaneous tumour (Fig. 1a′), which grew rapidly and became painful. CT revealed right cervical LN metastasis, and 2 swollen LNs, each measuring 17 mm were detected (Fig. 1c, d′). Avelumab was administered intravenously (10 mg/kg). RT (45 Gy) was performed for the left cheek and left cervical metastatic lesions. After 6 weeks of treatment (i.e. at the end of irradiation and after the third administration of avelumab), the left cheek tumour and left cervical LN metastasis decreased significantly in size (Fig. 1b′). The LN in the right cervical region, which had not been irradiated, became swollen, but decreased in size from 17 mm at the start of the treatment to 8 mm after treatment (Fig. S1c, f′). No side-effects associated with the treatment were observed. To date, administration of avelumab has been continued.

**DISCUSSION**

mMCC is a rare and aggressive type of skin cancer with poor survival outcomes (1). Although mMCC is a chemosensitive disease, durable responses are rare (2). Retrospective studies of first-line chemotherapy for patients with mMCC have reported median progression-free survival periods of 3.1–4.6 months (3, 4), highlighting...
MCC is a tumour that appears amenable to the abscopcal effect. Since MCC has high radiation sensitivity, the tumour cells are more prone to apoptosis than other carcinomas when exposed to RT. This may lead to cytotoxic T-cell activation via DAMPs and the production of various cytokines. Activated cytotoxic T cells and various cytokines exert antitumor immunity throughout the body, and it is considered that co-administration of ICI can enhance the efficacy of this process. Therefore, in patients with multiple metastases from MCC, an abscopcal effect can be expected, and ICI administration combined with RT should be considered. Although radiation has been employed as local therapy for MCC up to now, it may be developed as systemic therapy through antitumor immunity when used in combination with ICI. However, the number of reports documenting an abscopcal effect in mMCC is still limited (11–13). Bloom et al. (11) and Xu et al. (12) reported cases in which an abscopcal effect occurred through a combination of ICI and RT. On the other hand, Cotteter et al. (13) reported a case in which an abscopcal effect occurred only as a result of hypofractionated RT (12 Gy in 2 fractions) for cutaneous metastases in the lower limb. Bloom et al. (11) employed conventionally fractionated radiation (45 Gy in 25 fractions), whereas Xu et al. (12) used 8 Gy of irradiation in a single dose. In all of these cases, complete tumour regression was reported. All of the previous reports described complete regression of the tumour with no serious side-effects. Therefore, a combination of ICI and radiation therapy is a well-tolerated treatment. In order to establish effective combination therapy with ICI and RT, a number of issues still need to be clarified, such as the timing of combined use, the optimal total dose, and whether it should be fractionalized radiation or hypofractionated radiation. Therefore, studies of additional cases are required.

The authors have no conflicts of interest to declare.

REFERENCES

1. Schadendorf D, Lebbé C, Zur Hausen A, Avril MF, Hariharan S, Bharmal M, et al. Merkel cell carcinoma: epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer 2017; 71: 63–69.
2. Nghiem P, Kaufman HL, Bharmal M, Mahnke L, Phtatak H, Becker JC. Systematic literature review of efficacy, safety and tolerability outcomes of chemotherapy regimens in patients with metastatic Merkel cell carcinoma. Future Oncol 2017; 13: 1263–1279.
3. Cowey CL, Mahnke L, Espiritu J, Helwig C, Oksenh D, Bharmal M. Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with chemotherapy in the USA. Future Oncol 2017; 13: 1699–1710.
4. Iyer JG, Blom A, Doumani R, Lewis C, Tarabadkar ES, Anderson A, et al. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma. Cancer Med 2016; 5: 2294–2301.
5. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D’Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016; 17: 1374–1385.
6. Lim JY, Gerber SA, Murphy SP, Lord EM. Type I interferons induced by radiation therapy mediate recruitment and effector function of CD8(+) T cells. Cancer Immunol Immunother 2014; 63: 259–271.
7. Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J Exp Med 2006; 203: 1259–1271.
8. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopcal response to radiation and ipilimumab in a patient with metastatic non-small-cell lung cancer. Cancer Immunol Res 2013; 1: 365–372.
9. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, et al. Immunologic correlates of the abscopcal effect in a patient with melanoma. N Engl J Med 2012; 366: 925–931.
10. Trommer M, Yeo SY, Persighel T, Bunck A, GrÜll H, Schlaak M, et al. Abscopal effects in radio-immunotherapy-response analysis of metastatic cancer patients with progressive disease under anti-PD-1 immune checkpoint inhibition. Front Pharmacol 2019; 10: 511.
11. Bloom BC, Augustyn A, Pezzi TA, Menon H, Mayo LL, Shah SJ, et al. Rescue of immunotherapy-refractory metastatic Merkel cell carcinoma with conventionally fractionated radiotherapy and concurrent pembrolizumab. Front Oncol 2019; 9: 223.
12. Xu MJ, Wu S, Daud AI, Yu SS, Yom SS. In-field and abscopcal response after short-course radiation therapy in patients with metastatic Merkel cell carcinoma progressing on PD-1 checkpoint blockade: a case series. J Immunother Cancer 2018; 6: 43.
13. Cotteter SE, Dunn GP, Collins KM, Sahni D, Zukotynski KA, Hansen JL, et al. Abscopcal effect in a patient with metastatic Merkel cell carcinoma following radiation therapy: potential role of induced antitumor immunity. Arch Dermatol 2011; 147: 870–872.