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Immunotherapy with imiquimod and interferon alfa for metastasized Merkel cell carcinoma

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ABSTRACT

Merkel cell carcinoma (MCC) is a highly aggressive neuroendocrine tumour of the skin. Remission rates are high with chemotherapy in patients with metastasis, but without any improvement in overall survival.

We present the case of a 90-year-old woman with facial MCC. After radiation and surgery, the MCC recurred with widespread cutaneous and regional lymph node metastases. The metastases were treated with weekly intralesional injections of $1–2\times10^6$ IU interferon alfa-2a, accompanied by topical imiquimod 5% cream 3 times weekly. After partial regression, subcutaneous pegylated interferon alfa-2b was added at a dose of 30 μg weekly, which was then increased to 50 μg weekly. At 4 months after the start of immunotherapy, all cutaneous metastases and the intralesionally treated lymph node metastases receded. Interruption or reduction of systemic interferon application resulted in locoregional relapses that were successfully treated with surgery or intralesional interferon injections. The patient remains alive 30 months after initiation of immunotherapy, suggesting that locally metastasized MCC might be able to be controlled with local and systemic immunotherapy.

Key Words Merkel cell carcinoma, immunotherapy, interferon, imiquimod

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INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and highly aggressive neuroendocrine tumour whose cells resemble the mechanoreceptor Merkel cells of the skin[1]; however, the true origin of MCC is still debated. It occurs mostly in elderly and immunosuppressed patients and appears mainly in sun-exposed areas[2].

In most cases of histologically typical MCC, the carcinoma seems to be induced by infection with a polyomavirus that was first isolated from a MCC and was accordingly named "Merkel cell polyomavirus"[3]. Viral DNA has been detected in about 80% of all analyzed MCCs[4]. Transcription of the viral oncogene (Merkel cell polyomavirus T antigen) was demonstrated to be essential for Merkel cell polyomavirus–induced Merkel cell carcinogenesis[5]. The molecular mechanisms responsible for virus-negative MCC have yet to be determined.

Merkel cell carcinoma has a mortality rate of up to 33% within 3 years[6]. Because of its rareness and untypical appearance, diagnosis of MCC is often delayed. To reduce the risk of metastasis, wide surgical excision with sentinel lymph node biopsy and adjuvant radiotherapy for the excision site and the regional drain area have been recommended. When metastasized, the mortality rate of MCC increases to 90% within 3 years[6].

Various chemotherapy regimens have been used in MCC, including agents such as cyclophosphamide, doxorubicin, vincristine with or without prednisolone, etoposide, cisplatin, and carboplatin[7]. High remission rates are reported after chemotherapy; however, no improvement in overall survival has been achieved[6,7]. Several experimental treatments with immunomodulatory drugs and with molecularly-targeted agents have been tried with moderate success[8–14]. Here, we report the case of an elderly woman with regionally metastasized MCC that responded to a combination of local skin-directed, intralesional, and systemic immunotherapy.

CASE DESCRIPTION

A 90-year-old white woman was referred to our clinic after a MCC lesion had been removed from the right side of her nose near the corner of the eye. Histopathologic

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examination revealed incomplete tumour excision. Given her significant comorbidity (moderately severe combined aortic and mitral valve disease), the patient refused surgery. Radiotherapy (30 Gy) was provided to the site of the primary tumour.

After 5 months, the patient developed a cutaneous satellite metastasis, which was surgically excised. A year later, surgery and adjuvant radiation of the regional drain area were performed to treat 3 in-transit metastases on the right cheek.

At age 92, the patient presented to our clinic with multiple in-transit metastases on the right cheek [Figure 1(A)], a right submandibular lymph node metastasis, and a cutaneous metastasis on the left upper eyelid. Computed tomography did not reveal any pulmonary, abdominal, or cerebral metastases. However, surgery was not performed because of the extensive spreading in the affected area and because of reduced cardiac function, with N-terminal pro brain natriuretic peptide in the 900–2400 pg/mL range. Radiation could not be given because the area had already been irradiated.

Histology of the first cutaneous in-transit metastasis revealed typical MCC with positivity for cytokeratin 20 [Figure 2(A)], chromogranin, synaptophysin, and CD56 (antibodies provided by Dako, Glostrup, Denmark), as well as positivity for Merkel cell polyomavirus (antibody CM2B4: Santa Cruz Biotechnology, Santa Cruz, CA, U.S.A.)[15]. The proliferation rate was high, with 60%–70% Ki-67 staining (Dako) [Figure 2(B)]. The metastasis demonstrated significant lymphocytic infiltration, which is regarded as a favourable prognostic sign[16]. Infiltration was predominantly CD3- and CD4-positive [Figure 2(C)]. Only a few infiltrating cells demonstrated CD20 or CD8 positivity [Figure 2(D)] (antibodies provided by Dako).

Infiltration by immune cells was considered a favourable prognostic sign despite the high proliferation rate of the tumour. After interdisciplinary tumour board presentation, off-label intralesional treatment with 1–2×10^6 IU interferon alfa-2a once weekly, accompanied by topical imiquimod 5% cream 3 times weekly, was initiated because of favourable case reports in the literature[8–14].

Within 1 month, that regimen resulted in a small reduction in the size of some, but not all, the injected metastases. Treatment was well tolerated, and the imiquimod was noted to induce a perilesional eczematous reaction as previously described[8] [Figure 1(B)]. Partial regression was considered proof of the efficacy of the immunologic approach, and so subcutaneous pegylated interferon alfa-2b (INFα2b) 30 μg once weekly was added (Figure 3). In addition, regular medication with simvastatin was stopped because of the putative association between MCC and statin use[17].

During the first 2 months of treatment with subcutaneous pegylated interferon, metastases further increased in size, and the dose was raised to 50 μg once weekly (Figure 3). The patient then developed an episode of fever and malaise, after which all cutaneous metastases and the intralesionally treated right-sided submandibular metastasis receded within 2 weeks (Figure 4). Intralesional and systemic interferon treatment was then stopped, but 3 months later, a left-sided submandibular lymph node metastasis was palpable. In hindsight, the metastasis was already present before interferon treatment, as demonstrated by magnetic resonance imaging.

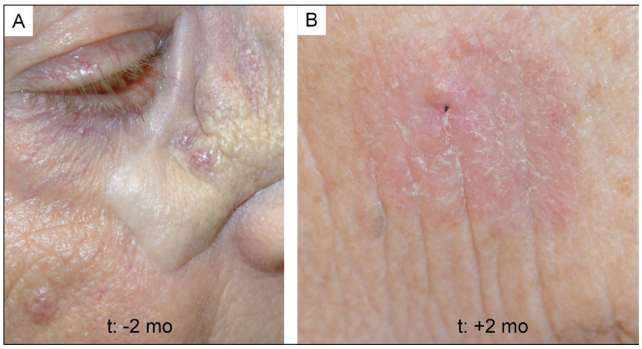

FIGURE 1 (A) Initial presentation of multiple in-transit metastases before immunotherapy. (B) Local reaction after 2 months of intralesional interferon alfa and imiquimod 5% cream immunotherapy.

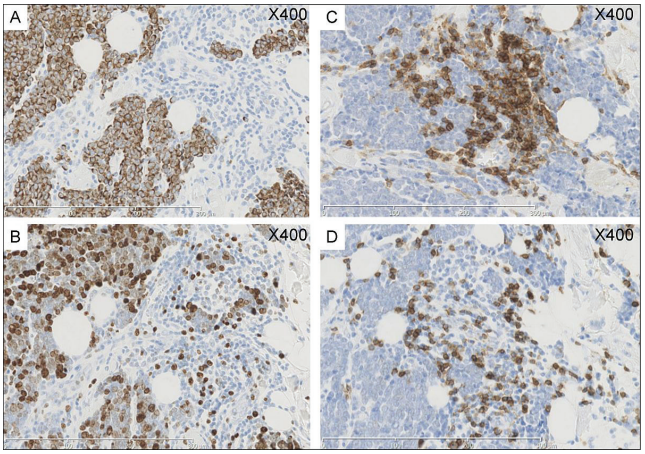

FIGURE 2 Immunohistochemistry of Merkel cell carcinoma metastases (400× original magnification). (A) Cytokeratin 20. (B) Ki-67. (C) CD4. (D) CD8.

After successful surgery, the patient continued to use local prophylactic treatment to the left cheek with imiquimod cream and to receive subcutaneous pegylated INFα2b at a reduced dose of 20 μg once weekly. After 3 months without evidence of recurrence, pegylated INFα2b was reduced to 20 μg every 2 weeks.

Two months later, and after a short interruption of systemic treatment, several cutaneous nodules up to 0.5 cm in size developed on the patient's left cheek. Those metastases regressed completely after 2 intralesional injections with 1–2×10^6 IU interferon alfa-2a once weekly. Subcutaneous pegylated INFα2b was again administered weekly.

Because of concurrent illnesses, pegylated interferon had to be interrupted several times, with subsequent recurrences of cutaneous metastases on both cheeks. Because of its larger size, one metastasis was surgically excised; the other metastases receded after intralesional interferon injections. Figure 3 correlates the approximate tumour burden over time with the various treatment modalities. Tumour volume was measured by ultrasonography or magnetic resonance imaging, and the volume of the skin metastases was

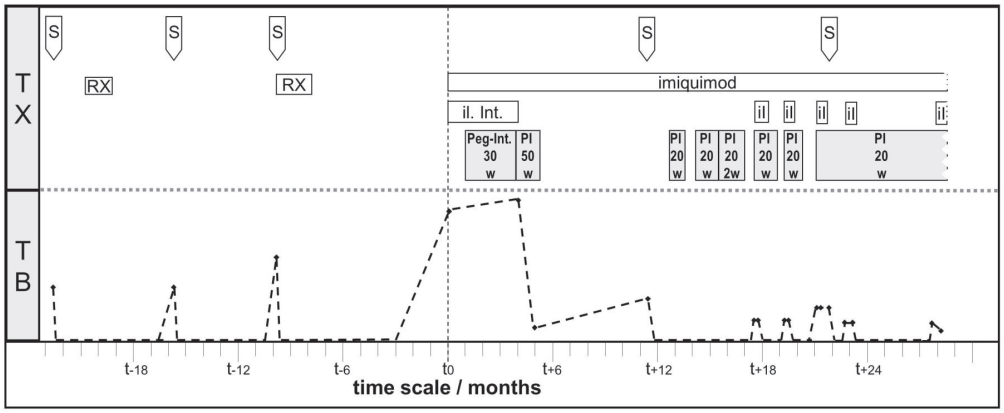

FIGURE 3 Clinical course of the patient. TX = therapies (S = surgery; RX = radiotherapy; il. Int. or iI = intralesional interferon alfa; Peg-Int. or PI = pegylated interferon afa). TB = tumour burden in cubic centimetres (approximate, semi-logarithmic scale).

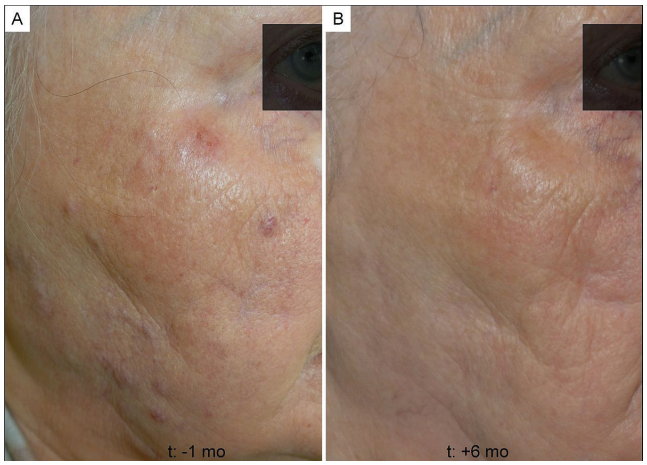

FIGURE 4 (A) Multiple in-transit metastases 1 month before therapy. (B) Complete clearance of cutaneous metastases after 6 months.

retrospectively estimated from photographs. The patient remains alive 52 months from diagnosis and 30 months after initiation of immunotherapy.

DISCUSSION

Immunologic treatment of MCC using interferons and the toll-like receptor 7 agonist imiquimod has been tried, with mixed response[8–14]. Epidemiologic and experimental evidence both strongly suggest that MCC is controlled by the immune system[18–22]. Advanced age and immunosuppression favour the development of MCC and are suggested to be responsible for a strong rise in the incidence of MCC since the mid-1980s[18]. Infiltration of MCC tissue by tumour-specific immune cells has been demonstrated[22]. A reversible immune escape mechanism by downregulation of MHC I has been detected within MCC[20], and types I and II interferons were shown to inhibit MCC *in vitro*[19,20].

Despite experimental and clinical evidence that MCC should respond to immunologic treatment with interferons or imiquimod, immunotherapy plays no major role in the treatment of metastasized MCC, and no immunotherapy regimens have been integrated within accepted guidelines[23]. The very low incidence of MCC, which still occurs at less than 1 case per 100,000 population per year in most parts of the world[24], and the resulting low numbers of patients with metastasized disease even in major institutions have, in the past, prevented the performance of large controlled immunotherapy trials and rational approaches to accepted immunologic treatment schedules. The recent rise in MCC incidence, combined with the arrival of new immunomodulatory drugs, has stimulated several new immunotherapy trials (see https://clinicaltrials.gov/ct2/results?term=merkel+cell+carcinoma), but still, immunologic treatment of MCC has, up to now, been based mainly on a few case reports and on the management of comparable immunologically controlled neoplasms such as malignant melanoma.

Likewise, the patient presented here was treated in our clinic with a combination of skin-directed, intralesional, and systemic immunotherapies commonly used for cutaneous metastases of malignant melanoma[25,26]. Our case highlights a common problem in patients with MCC metastasis: most are old and have significant comorbidities that limit the tolerability—and therefore the success—of aggressive chemotherapy and immunotherapy. The combination of local immunotherapy and low-dose systemic immunotherapy, as used in our patient, might represent an approach that enhances the tolerability and efficacy of immunotherapy. A recent publication used a similar approach of combined local and systemic immunotherapy for MCC and reported a favourable outcome[27].

In our patient, intralesional injections of interferon alfa-2a seem to have been essential to tumour clearance, because only the intralesionally treated lymph node metastases responded; the contralateral lymph node metastasis progressed despite systemic application of pegylated INFα2b. In addition, localized immunotherapy has the advantage of allowing for a comparison between treated and untreated metastases, which might provide an early indication of treatment response.

We opted for pegylated INFα2b once weekly because tolerability is better with the slow release of biologically active interferon from this modified form than with the

subcutaneous application of non-pegylated interferon alfa. For the same reason, pegylated INFα2b was started at a reduced dose. A response was observed only after 4 months of immunotherapy. The delay in response is not untypical for immunotherapy, and it underscores the necessity to treat patients for a sufficient length of time with an immunomodulatory drug. Reduction of the pegylated INFα2b dose and extension of the treatment interval both led to recurrence, suggesting that immunotherapy must exceed some threshold to be effective. Still, the multiple recurrences in our patient also suggest that the treatment did not definitively cure the disease. Nevertheless, given the poor prognosis in advanced MCC, tumour control by immunotherapy in our patient has to be considered a favourable outcome.

CONCLUSIONS

The case presented here demonstrates that patients with metastatic MCC and significant comorbidities might be successfully treated with immunotherapy that combines localized and systemic approaches and that favours duration of treatment over intensity of treatment. Given the proof-of-principle demonstrated by several case reports and *in vitro* experiments, adapted treatment schedules and the use of novel immunotherapies such as anti-CTLA4 and anti–PD-1 antibodies should be further examined in controlled studies so as to reduce mortality from metastatic MCC in future.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: AR has received speaker fees from Bristol–Myers Squibb and Roche Pharma AG.

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