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A 21-year course of Merkel cell carcinoma with adjuvant Viscum album extract treatment: A case report

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ABSTRACT

Background: Merkel cell carcinoma (MCC) is a rare, aggressive, neuroendocrine skin tumor with frequent local recurrence, lymph node involvement, distant metastasis, and a high mortality rate. Viscum album extracts (VAE) are a widely used adjunct in cancer treatment and show cytotoxic and immune-modulating effects.
Case presentation: A 64-year-old woman was diagnosed with a MCC of the left forearm. In the following course of 21 years, she experienced 4 episodes of lymph node relapse (axillary, submandibular, axillary, clavicular). All lesions were surgically excised. The patient declined chemotherapy and radiation and opted for adjuvant treatment with local subcutaneous VAE injections. Currently—21 years after first diagnosis and 9.5 years after the last relapse—the patient is tumor-free, in good health, and without functional limitations.
Conclusion: The presented case shows long-time survival in a patient with MCC treated with surgery and VAE injections. The immune system plays a key role in tumorigenesis of MCC. VAE enhances several immune pathways and might therefore contribute to immunologic tumor control in MCC. The role of VAE in MCC should further be investigated.

1. Background

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine tumor of the skin (incidence 0.1–0.3 new cases per 100 000/year.[1]) with a high rate of recurrence and metastasis. Risk factors are light skin, ultraviolet (UV) exposure, and immunosuppression (eg, organ transplantation, HIV infection, B-cell and other malignancies and maintenance treatment with m-TOR-inhibitors[2]). Merkel cell polyomavirus is involved in the carcinogenesis of MCC[3] Prognostic factors include low tumor stage at first diagnosis, localization of the tumor at upper extremities, female sex, age under 67 years, intact immune status,[4] and lymphocytic infiltration of the tumor tissue.[5] Ten-year survival rates vary depending on stage of disease, from 71% in localized disease to 20.1% in metastatic disease. Treatment for MCC is wide-margin surgery with subsequent radiation. Chemotherapy for advanced MCC is controversial.[6] Immune therapies show promising results in MCC,[7] and the PD-L1 inhibitor avelumab was recently approved for the treatment of MCC in the United States.[8] Spontaneous regression of MCC has been reported – this event occasionally occurred after biopsy of the tumor or reversal of immunosuppression.[9]

Viscum album extract (VAE) therapy is a widely used adjunct to standard cancer therapy. VAE show cytotoxic and apoptogenic effects in cancer cells. Immune-modulating effects of VAE have been observed in in vitro and animal studies (activation of monocytes/macrophages, granulocytes, natural killer cells, T cells, dendritic cells, and release of a variety of cytokines). VAE also reduce tumor-induced immunosuppression.[10,11]

VAE are usually applied subcutaneously, starting with a low dose, which is then slowly increased. Common side effects are local skin reactions and flu-like symptoms; VAE are otherwise safe, even when used at higher dosages.[12] Clinical studies found an improvement in quality of life and, in some cases, in survival.[13,14] Complete durable tumor regression under VAE treatment has been reported in case reports for cutaneous squamous cell carcinoma,[15] MCC [16], melanoma,[17,18] and others—usually resulting from local and high-dosage application.

2. Case presentation

A 64-year-old woman discovered a 1 × 0.4 cm lesion of the skin on her left forearm. The lesion was excised and histologically diagnosed as

Abbreviations: CT, Computed tomography; HIV, Human immunodeficiency virus; MCC, Merkel cell carcinoma; UV, Ultraviolet; VAE, Viscum album extracts

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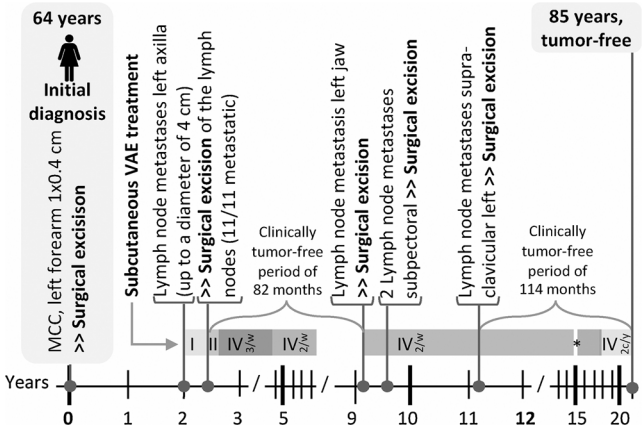

Fig. 1. Timeline of the patient with Merkel cell carcinoma.

Table 1
Course of the Viscum album extract (VAE) therapy

Month	VAE Series[a] (mg)	Application	Number of Applications[b]
1[c]–4	I (1/5/10)	3x/Week	42
5–6	II (10/20/30)	3x/Week	14
6–24	IV (20/30/50)	3x/Week	182
25–74	IV (20/30/50)	2x/Week	168
74–86	Treatment Break		
87–156	IV (20/30/50)	2/Week	476
157–160	Treatment Break		
161–192	IV (20/30/50)	2/Week	210
193–228[d]	IV (20/30/50)	2 Cycles per Year	84
			Total: 1176

[a] I: Helixor® A (from the host tree fir) Serie I contains 7 vials of lower dosage (3 × 1 mg/mL, 3 × 5 mg/mL, 1 × 10 mg/mL); II: Serie II contains 7 vials of medium dosage (2 × 10 mg/mL, 2 × 20 mg/mL, 3 × 30 mg/mL); IV: Serie IV contains 7 vials of higher dosage (2 × 20 mg/mL, 2 × 30 mg/mL, 3 × 50 mg/mL).

[b] Applications were carried out as 7 subcutaneous injections in increasing dosages (Series I, II or IV) followed by 7 injections in decreasing dosages (Series I, II or IV, each backwards), with a subsequent treatment break of 2 weeks.

[c] Month 1 of the VAE therapy = Month 25 after the initial diagnosis.

[d] Until the date of publication.

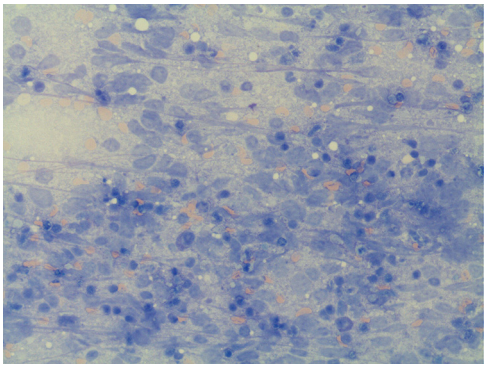

Fig. 2. Submandibular metastasis of the patient: Small monomorphic tumor cells with little cytoplasm; the nuclei are roundish with finely granulated chromatin structure of the chromatin and small nucleoli. Pappenheim stain, 1:200.

Merkel cell carcinoma (T1, N0, M0, R0). The patient was Caucasian, had been working as an employee in the city council, had a normal body weight, was a non-smoker, and had no history of excessive UV exposure or immune suppression. Her maternal grandfather had stomach cancer and a paternal aunt, colon cancer. Shortly before the initial diagnose of MCC, her husband had died. Two years after the initial MCC diagnosis, the patient noticed enlarged lymph nodes in the left axilla, which were diagnosed as lymph node metastases by computed tomography (CT) scan and fine-needle aspiration cytology. The patient requested complementary cancer treatment, and subcutaneous injections with VAE (Helixor® A) were started distal from the location of the primary tumor (Fig. 1, Table 1). Eleven axilla lymph node metastases with a diameter of up to 4 cm were subsequently excised. The patient rejected radiation and chemotherapy, which were recommended in view of the high risk of recurrence. She continued the VAE treatment for 70 months without any sign of cancer recurrence. Another 12 months later, a new lesion appeared in the angle of the left jaw (submandibular); it was excised and diagnosed as metastasis of the MCC (Fig. 2). The VAE treatment was started again as subcutaneous injections in the region of metastasis (Fig. 1, Table 1). Four months later, another two metastases appeared under the M. pectoralis minor of the left side and were excised. Twenty months later, further metastases appeared on the patient's left supraclavicular, and these were excised. Despite these relapses, VAE treatment was continued in the same regimen in the region of the metastases. In regular clinical and ultrasound examinations of the regions of metastasis as well as the organs of the abdomen, no additional tumors were found. During the course of treatment, the patient sustained a femoral neck fracture and subdural hematoma after a fall and underwent hip replacement and trepanation; during these procedures, no metastases were found in x-rays of the lung and bones.

Currently—nearly 10 years after the last relapse and 21 years after first diagnosis–the patient, who is now 85 years of age, is healthy, without functional limitations, and tumor free. She manages her own household and occasionally takes care of her grandchildren. The patient experienced no side effects of VAE treatment: no fever and no noticeable skin reactions.

3. Further diagnoses and therapies

The patient is treated with enalapril and irbesartan for hypertension and with levothyroxin for a thyroid struma. Aside from surgery and VAE treatment, no other tumor-specific therapy was used.

4. Discussion and conclusions

The presented case describes a 21-year course of treatment of a patient with MCC with 4 lymph node relapses with several nodes involved. The only therapies used were local excision and continuous subcutaneous VAE injections. The patient had long relapse-free periods (82 months and 114 months), long survival (21 years currently), and only minor limitations of quality of life and has now been tumor free for nearly 10 years at the time of publication of this report. For the duration therapy, she had only minor limitations in her daily activities.

As VAE therapy was used in combination with surgical excision in this case, its influence on the success of the treatment cannot conclusively be defined. However, considering the extent of metastatic disease and involvement of several lymph node regions, the contribution of VAE to the long tumor-free periods and the long-term survival can be assumed.

Orange et al. reported another case of a patient with MCC in which VAE treatment alone led to a complete remission of an axillary lymph node relapse. Contrary to our case—in which only subcutaneous injections and relatively low dosages were used–Orange used higher dosages and combined subcutaneous, intravenous, and intralesional applications, which led to self-limiting episodes of high fever (up to 39.4 °C) and localized skin inflammation.[16]

Immunosuppression and escape from immune system mechanisms play key roles in tumorigenesis and the development of MCC.[7] VAE acts through stimulation of dendritic cells and enhancement of antigen processing and of the T-cell response as well as through strong

stimulation of the innate immune system (natural killer cells, monocytes/macrophages, granulocytes).[10,19] Through these mechanisms, VAE may have contributed to immunologic tumor control in this case.

As MCC is a rare cancer and clinical trials are difficult to perform, further cases of VAE use in MCC should be carefully documented and published to help to determine whether further investigation of the use of VAE in MCC treatment is worthwhile.

Consent to publish

Written informed consent was obtained from the patient for publication of this case report and accompanying images. She read the final version of this article and confirmed its content.

Availability of data and materials

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

PGW, LK, and GSK contributed to the case report design. LK was the physician in charge who provided the patient's information. PGW and LK collected and provided the data. PGW was the principle author of the paper, had full access to all data, and is guarantor. LK provided specific knowledge in mistletoe treatment. GSK supervised the report writing and the publication process. All authors approved the final manuscript.

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This case report was prepared following the CARE Guidelines.[20]

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