Combined treatment with radiotherapy, chemotherapy and avelumab results in regression of metastatic Merkel cell carcinoma and improvement of associated Lambert-Eaton myasthenic syndrome: A case report

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Received April 28, 2022; Accepted August 30, 2022

DOI: 10.3892/ol.2022.13513

Abstract. Merkel cell carcinoma (MCC) is a rare and highly aggressive neuroendocrine malignancy arising from mechnoreceptors in the basal epidermis. Due to a pronounced risk of spread and a high propensity for recurrence after treatment, immediate treatment is of utmost importance. Lambert-Eaton myasthenic syndrome (LEMS) is a paraneoplastic phenomenon affecting the muscles with autoimmune pathophysiology, and >50% of known cases are associated with an underlying malignancy. In the present report, the case of a 67-year-old man presenting with progressive proximal muscle weakness, autonomic dysfunction and involuntary weight loss is described. Symptoms and detection of voltage-gated calcium channel antibodies were consistent with LEMS. Distant metastases were found in the inguinal and iliac lymph nodes, and these were immunohistochemically confirmed to be of epithelial and neuroendocrine origin, consistent with MCC. Local radiotherapy and chemotherapy improved the symptoms; however, a change of treatment was required due to the side effects of the chemotherapy. Avelumab, an immune checkpoint inhibitor, was therefore introduced, and within a year the patient did not only experience tumor remission but also exhibited marked improvements in muscle strength and mobility. At present, 2 years later, the MCC is still in remission. To the best of our knowledge, the present report is the first to describe MCC with associated LEMS, which was successfully treated with avelumab after previous radiotherapy and chemotherapy, with both improved functional motor recovery and tumor reduction. In conclusion, the present case report demonstrated that the present treatment strategy is a potential treatment option and could thus be considered in similar cases.

Introduction

Merkel cell carcinoma (MCC) is a rare and highly aggressive neuroendocrine malignancy thought to be arising from mechnoreceptors in the basal epidermis. It has also been discussed in the literature that Merkel cells might not be the cell of origin in MCC, but instead derived from epidermal stem cells or other primitive totipotent stem cells that under malignant transformation gain neuroendocrine characteristics (1). This theory is partly considered due to various expression patterns of immunohistochemically markers, and in some patients MCC are found concomitant with other epithelial lesions like basal cell carcinoma or squamous cell carcinoma in the same area (2). Therefore, the term 'primary neuroendocrine carcinoma of the skin (PNECS)' has been suggested as an alternative nomenclature. MCC is associated with Merkel cell polyomavirus (MCPyV) and UV exposure, and other risk factors include age, Caucasian skin type, and immunosuppression (e.g. HIV or transplant recipients) (3). It most commonly presents as rapidly growing and painless nodules in the skin of the face and neck, but lymph node metastases without a primary localization have also been reported (4). MCC belongs to the small cell carcinoma family shared with small cell lung carcinoma (SCLC), carcinoids and medullary carcinoma of the thyroid, but despite the similarity, paraneoplastic syndromes are rarely seen in MCC, and instead are more commonly reported in SCLC (5). It spreads rapidly to distant lymph nodes and has a high propensity for recurrence following treatment, with an overall 5-year survival rate of 0-18% in patients with distant metastases (6). With better results in survival rate, avelumab (FDA-approved 2017) is now used as a monotherapy for adults with metastatic MCC (6). It targets the programmed death-ligand (PD-L1), which in several cases is upregulated on tumor cells to inactivate T-cells, and underlies the mechanism by which the tumor cells evade the immune system. PD-L1...
inhibition with avelumab makes it possible for the continued recognition of tumor cells as foreign by T-cells and thus for effective elimination of the tumor (7).

Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of neuromuscular transmission, which is caused by antibodies against the P/Q-type voltage-gated calcium channels (VGCC) on the presynaptic nerve terminals. This impairs the release of acetylcholine and results in a poorly transmitted action potential with ensuing muscle weakness. LEMS usually presents with areflexia, proximal muscle weakness (especially in the lower limbs) and autonomic dysfunction (8). More than 50% of cases are associated with underlying malignancies (primarily SCLC), which express functional VGCCs (9). Diagnosis is confirmed using electromyography, clinical examination, and detection of antibodies; however, ~15% of patients with LEMS lack these antibodies, thus these criteria alone cannot be used to exclude a diagnosis (8). Treatment of underlying malignancy can often reduce the muscular symptoms, but complementing treatment with 3,4-diaminopyridine (and sometimes also immunosuppressants and pyridostigmine) is usually essential (10).

**Case report**

The patient presented has provided written informed consent for publishing his data and associated images (documented in his patient files), and all reporting and operational procedures were performed in accordance with the Declaration of Helsinki. In January 2018, a 67-year-old man presented with around a 1-year history of progressive muscle weakness and involuntary weight loss. The weakness was most prominent in the lower limbs, which had made him wheelchair-bound over the last few months. He also reported dry mouth, erectile dysfunction, and constipation as signs of autonomic dysfunction. There was no previous history of malignancy, but he was an ex-smoker with 25 previous pack-years and was obese with hypertension at the time of presentation.

In March of the same year, clinical examinations were performed, and together with elevated titer of P/Q-type VGCC-antibodies in serum (65.2 pmol/l, ref <40), a diagnosis of LEMS was confirmed and symptomatic treatment with 3,4-diaminopyridine and pyridostigmine was initiated. Since LEMS is strongly associated with malignancy, CT thorax/abdomen, ultrasound of scrotum, and 18-FDG-PET/CT were performed. No primary tumors on the skin were identified. There was no previous history of malignancy, but he was an ex-smoker with 25 previous pack-years and was obese with hypertension at the time of presentation.

The detailed experimental procedure of the PCR has been described previously (11). Presence of MCPyV was confirmed, and together with the ELECTHIP criteria (discussed further below), MCC was considered the most plausible diagnosis. Due to the dot-like positive staining of TTF-1, the conclusion from the multidisciplinary team meeting was to consider the staining as positive, but the antibody clone used at that time in our lab is known to crossreact with MCC with this staining pattern. Thus, the diagnosis of MCC was still considered the most likely despite that TTF-1 positivity very rarely is seen in MCC (12).

In April 2018, 3 months after the first radiological examinations, the patient had difficulty breathing. CT imaging showed no signs of lung metastases or pulmonary embolism, but a discrete progression of the largest node adjacent to the right acetabulum was observed. At this point, the patient was sent to the Oncology Department to receive local radiation therapy (3 Gy x 13 fractions) directed towards the enlarged iliac node and the groin area. About 1 month later, the patient exhibited some regression of the symptoms, but still experienced morning stiffness and muscle weakness. In June 2018, during the final weeks of radiation therapy, the muscle weakness gradually improved, and the VGCC-antibody titer were reduced (47.7 pmol/l, ref <40).

A further CT thorax/abdomen showed some regression of two of the nodes, but the results were not satisfactory enough and further treatment options were required. Chemotherapy with carboplatin/etoposide was considered, but this was based primarily on the indications to treat the paramalignant phenomenon and not to treat the malignancy itself. Because of its recommendations as an effective treatment for metastatic MCC, avelumab was determined to be the optimal treatment of choice. Due to the unavailability of avelumab at the time of initiation of therapy, carboplatin/etoposide was given at full dose (carboplatin AUC5 day 1 and etoposide 100 mg/m² days 1-3 in 21 day cycles) instead. Shortly after the first dose, the patient developed neutropenic fever and required antibiotic treatment. Due to the neutropenia, the next chemotherapy was therefore reduced to 80% of the dose, and the third and fourth doses were further reduced to 75%. After ~3 months
of chemotherapy, the neutrophil count remained low, and unfortunately, the overall results from the chemotherapy were not satisfactory in terms of symptom reduction of LEMS. The muscular symptoms gradually improved with chemotherapy and the P/Q-type VGCC antibodies were not detectable anymore on follow-up tests, but at the end of treatment the symptoms started to recur and progress again. Shortness of breath was once again reported, but this time a pulmonary embolism was detected.

These side effects highlighted the need for alternative treatment options, and at this point, in October 2018, avelumab was available. A total of 800 mg avelumab was given intravenously at 2-week intervals, with paracetamol 500 mg x2 and cetirizine 10 mg x1 as pre-medications 1 hour before treatment. In December 2018, the patient experienced further improvement in muscle strength and no side effects. Another 5 months later he was able to walk without aids. In June 2019, after 8 months and administration of 16 doses, a new radiological examination showed a distinct reduction in the size of the metastases, and it was decided that the treatment with avelumab should continue every second week for as long as no serious side effects occurred. Unfortunately, after about 1 year of avelumab infusions, the patient was diagnosed with suspected drug-induced hypothyroidism after presenting with high TSH and low T4 values. Levothyroxine was prescribed and treatment with avelumab was continued. A CT thorax/abdomen follow-up after 10 weeks presented lung infiltrations in the lower right lobe, as well as lateral and subpleural infiltrates in both upper lobes. There was no metastatic suspicion, but findings consistent with pneumonitis provided suspicion of another inflammatory drug-induced side effect. Since the treatment at this time had been administered for almost 1.5 years with no signs of recurrence, but with upcoming most likely drug-induced inflammatory side-effects such as hypothyroidism and pneumonitis, the decision was made to end the treatment. 3,4-diaminopyridine and pyridostigmine were to be continued, and radiological follow-up with 3-month intervals.

In April 2022, more than 2 years after the last dose of avelumab, the patient had no clinical or radiological (CT thorax/abdomen) signs of recurrence. The pulmonary infiltrates were gone, but a new case of pulmonary embolism had arisen during the follow-up period. With this exception, the patient was healthy with few signs of recurrent muscle weakness. As a follow-up, clinical and radiological examinations

### Table I. Primer and probe sequences (5'-3') used for detection of MCPyV.

| Primer description                              | Primer name | Sequence (5'-3')            |
|------------------------------------------------|-------------|-----------------------------|
| Forward primer of small T region               | MCPyV-5009.F| GTTCTGCACAGCATGTTAGGCT      |
| Reverse primer of small T region               | MCPyV-4890.R| AAACCTTCCAAGTAGGAGAA         |
| Probe of small T region                        | MCPyV STp   | GCTATCAGTGCTTTATTCTTGG     |
| Forward primer of viral protein 1 region       | MCPyV-1682.F| AGGCCTAGTGTATGATTACAGCAC   |
| Reverse primer of viral protein 1 region       | MCPyV-1780.R| CTTGTGGATCTAGGCGGT          |
| Probe of viral protein 1 region                | MCPyV VP1p  | ACAAATGGTGCCCTATTAC         |

The detailed PCR protocol has been described previously (11). MCPyV, Merkel cell polyomavirus.

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![Figure 1. Immunohistochemistry from the node in the groin. (A) Routine staining with hematoxylin-eosin (20x magnification) and (B) routine staining with hematoxylin-eosin at higher magnification (40x magnification) from the node in the groin. (C) The node was considered negative for chromogranin A (10x magnification), and positive for (D) thyroid transcription factor-1 (10x magnification), (E) synaptophysin (10x magnification) and (F) cytokeratin 20 (40x magnification).](image-url)
Discussion

In the present report, the case of a 67-year-old patient with pronounced paraneoplastic muscle symptoms arising from an uncommon cutaneous neuroendocrine tumor is described. MCC can present as a lymph node metastasis without a primary tumor or a cutaneous tumor, and it can therefore be hard to distinguish MCC from other neuroendocrine carcinomas. The distinction in diagnosis is important due to the completely different approaches to therapeutic management and outcomes (13,14). In a large study published in 2017, it was found that MCC (both with and without a primary tumor) could be distinguished from lymph node metastases caused by other neuroendocrine carcinomas using seven different criteria: Elderly age, Location of the tumor, Extent of the disease, Cytokeratin expression, TTF-1 expression, Histologic type and Merkel cell Polyomavirus detection, abbreviated as ELECTHIP (13). The study concluded that all patients with MCC had at least five of these criteria, while almost everyone (except one patient) with other neuroendocrine tumors had three or fewer. However, several MCC tumors without a known primary tumor had four criteria, and this was taken into consideration when diagnosing our patient (13). To summarize these criteria, the ‘normal’ pattern of MCC is: Age >70 years, tumors localized to the inguinal or parotid area, disease extent localized to a single lymph node area rather than systemic spread, positive staining for CK20, and most commonly negative staining for TTF-1 (15). MCC is a small cell carcinoma, while other neuroendocrine carcinomas may be small cell, large cell, or well-differentiated. A total of 80% are positive for MCPyV (16). Interestingly, MCPyV-positive tumors are associated with better 5-year survival rates and are less likely to have spread at diagnosis compared with MCPyV-negative tumors (17). Although the presence of MCPyV was used as one of the criteria, the possibility of a false positive PCR should not be overlooked (18). To minimize for this uncertainty, appropriate positive (plasmid pMCV-R17a) and negative (material from empty paraffin-block treated in the same way as the patient sample) controls where used when analyzing the sample. This uncertainty was also considered during the diagnostic workup by the multidisciplinary team meeting. Our patient matched four of these seven criteria: Tumor localized to the inguinal area, CK20 positivity, small cell histology, and detectable MCPyV. The slightly enlarged nodes in the axilla and mediastinum were not confirmed as malignant, thus the extent of the disease was most likely localized to two adjacent lymph node areas (Table II). In the present case, markers including CK20 and TTF-1 (normally used to distinguish MCC from other small cell carcinomas like SCLC) did not provide concrete guidance for an MCC diagnosis. TTF-1 is selectively expressed in the thyroid and pulmonary epithelial cells, while CK20 stains positive for Merkel cells and some other cells in the GI tract. SCLC is therefore usually CK20 negative and TTF-1 positive, whereas MCC exhibits the opposite pattern (negative for TTF-1 and positive for CK20) (19). Chromogranin A is also a typical positive neuroendocrine marker, that in our case, was negatively stained, and together with TTF-1 positivity, made the conclusion of diagnosis more difficult. The ELECTHIP-criteria were therefore a useful tool in this case when normal immunohistochemical staining patterns were absent, and no primary tumor was located. However, it should be noted that the diagnosis of MCC in this case remains uncertain since there is no evidence of primary cutaneous tumor. The diagnostic workup could possibly have been completed with Gallium-DOTATOC PET/CT which could have added valuable information. This was not done in our patient. It would possibly not have added much information regarding the diagnosis, but rather function as a marker for presence of somatostatin receptors, and thus guide in choice of treatment with somatostatin receptor analogues and/or radionucleotide therapy (20).

The Nobel Prize in 2018 was awarded to Tasuku Honjo and James Allison for the discovery of the PD-1 molecule on T-cells. PD-1 is involved in immune suppression, which is one of the most important escape mechanisms used by certain tumor cells. The inhibition of inhibitory mechanisms leads to a more active immune defense against the cancer and prolongs overall survival significantly in cancer forms that previously had long-term survival rates in single-digit percentages (21). The use of these immune checkpoint inhibitors provides hope to patients that previously only had months left to live and lays the foundation for further research on how to modulate and strengthen our immune response, as the most effective treatment against cancer (21). Until recently, cytotoxic chemotherapy has been part of the standard treatment for patients with MCC, even though there is no scientific support for the effectiveness of this treatment, and the rates of relapse are high (3). MCC is considered a chemosensitive carcinoma, but a survival benefit has not been shown and responses to chemotherapy are usually not durable (22). In 2016, a foundational study was published regarding the use of avelumab as on treatment naïve patients and patients who had received previous chemotherapy with metastatic MCC (6). The results were promising; 32% objective responses (9% complete and 23% partial responses),

Table II. ELECTHIP criteria.

| Criteria          | Indicator          | Current case |
|-------------------|--------------------|--------------|
| Elderly age       | >70 years          | No           |
| Location of the tumor | Inguinal or parotid | Yes          |
| Extent of disease | Restricted to one lymph node area | No |
| Cytokeratin expression | CK20 immunopositivity | Yes |
| TTF-1 expression  | Immunonegativity    | No           |
| Histological type | Small cell carcinoma | Yes |
| Merkel cell polyomavirus detection | Detection on PCR | Yes |

The present patient matched four of the seven criteria. CK20, cytokeratin 20; TTF-1, thyroid transcription factor-1.
no treatment-related grade 4 events, and (compared to the relatively high incidence of toxicity-related morbidity of chemotherapy) acceptable side effects. The study also showed almost twice as good results in patients with just one previous line of treatment, compared to the patients that did receive two or more.

The question was therefore raised if it may be more effective to start the treatment earlier with fewer previous cycles of cytotoxic treatment, since a functional immune system is necessary for the best possible response. For example, it has been reported that MCC developed shortly after the use of the TNF-a inhibitor adalimumab, which also suggests the importance of immunosuppression. In our case, chemotherapy was initiated due to the unavailability of avelumab. Chemotherapy treatment had to be stopped after four cycles due to neutropenia. Since the patient still had symptoms and the disease was progressing at the time, we decided to administer additional treatment with avelumab. Inflammatory side effects that presented after initiation of avelumab included pneumonitis, pulmonary embolism, and hypothyroidism. Most side effects are well known and tolerable, except for the neutropenia experienced by our patient. Pneumonitis occurred after ~1 year with avelumab and resulted in the termination of the treatment, but disappeared almost immediately after that. Pulmonary embolism, on the other hand, occurred after the end of treatment.

In 2020, the first publication of a case with MCC and paraneoplastic LEMS treated with avelumab was reported, to the best of our knowledge (23). In this report, the patient had a severe reduction in vital capacity, and the muscular symptoms initially worsened instead of improved after infusion. Additional immunoglobulins had to be added to manage these severe immunological side effects, but after that, the LEMS improved and the MCC went into remission. In our patient, even though he previously had received both chemotherapy and radiation therapy, there was no need for additional immunoglobulins, and the LEMS continued to improve after the introduction of avelumab. Previously, there have also been concerns that treatment with drugs potentiating the immune system may worsen the paramalignant symptoms, that was, however, not noted in our patient.

In the literature, we found four case reports with an association between MCC and LEMS (24-27). To summarize, in most cases treatment of the tumor reduced the LEMS-associated symptoms but none of these cases received treatment with avelumab. Some other case reports raises the concern regarding whether immunotherapy may cause LEMS (28-32), none of these are reported having MCC. The majority of the cases described had lung cancer and out of the case reports one cannot say whether LEMS was caused by the immunotherapy, only that it presented after initiation of treatment. However, those patients with onset after start of immunotherapy generally had less effect when treating the LEMS-symptoms.

In conclusion, signs indicative of LEMS should always form the basis for a thorough malignancy screening even if lung examinations appear normal. The effect of the combined treatment with radiotherapy, chemotherapy, and avelumab, as well as the tolerance in our patient suggests that this might be a suitable treatment strategy for other patients with MCC combined with LEMS.

Acknowledgements

The authors would like to thank Dr Daniel Nosek (Department of Medical Biosciences, Umeå University, Umeå, Sweden) for his technical assistance with Figure 1.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors’ contributions

CG, MIM, CK, TR, TD, PI and DL contributed to acquisition, analysis and interpretation of the patient data presented in this case report. CG and DL drafted the manuscript. All authors have made critical revisions. All authors read and approved the final manuscript. CG and DL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The patient has provided written informed consent to participate.

Patient consent for publication

The patient has provided written informed consent for publication of the data in this manuscript.

Competing interests

The authors declare that they have no competing interests.

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