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

CAROLINE GREEN[1], MARTIN ISAKSSON METTÄVAINIO[2], CHRISTINA KJELLMAN[1], TORBJÖRN RAMQVIST[3], TINA DALIANIS[3], PERNILLA ISRAELSSON[4] and DAVID LINDQUIST[1]

Departments of [1]Clinical Sciences and [2]Medical Biosciences, Umeå University, SE-90187 Umeå; [3]Department of Oncology-Pathology, Karolinska Institute, SE-17177 Stockholm; [4]Department of Radiation Sciences, Umeå University, SE-90187 Umeå, Sweden

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Abstract. Merkel cell carcinoma (MCC) is a rare and highly aggressive neuroendocrine malignancy arising from mechanoreceptors 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.

Correspondence to: Dr David Lindquist, Department of Clinical Sciences, Umeå University, By 29 NUS, SE-90187 Umeå, Sweden
E-mail: david.lindquist@umu.se

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Introduction

Merkel cell carcinoma (MCC) is a rare and highly aggressive neuroendocrine malignancy thought to be arising from mechanoreceptors 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 titers 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. Slightly enlarged nodes were observed in the left axilla and mediastinum, and more prominent nodes were observed in the right groin area. The 18-FDG-PET/CT presented increased activity in a small area of the prostate, but urological examinations ruled out malignancy. Additionally, four areas with increased metabolism were also detected in both the right groin and iliac lymph nodes: A 3.5 cm node along the right external iliac artery, a 1.7 cm node deeply located, a 3 cm node superficially located, and lastly a node in an area dorsally and adjacent to the left ischial bone.

Extirpation of one of the nodes in the right groin was performed, and immunohistochemically stained preparations showed markers associated with neuroendocrine tumors, with the exception of chromogranin-A. Staining was positive for AE1/AE3 (Dako M3515, clone AE1/AE3, dilution 1:50), synaptophysin (Novocastra NCL-L-synap-299, clone 27G12, dilution 1:50), CD56 (Cellmarque 156R-94, clone MRQ42, dilution 1:500), and TTF-1 (Novocastra NCL TTF-1, clone SPT24, dilution 1:100), and dot-like positive for CK20 (Dako M7010, clone Ks20.8, dilution 1:25). Chromogranin A (Roche 760-2519, clone LK2H10, no dilution) was negative and Ki-67 (Roche 790-4286, clone 30-9, no dilution) was positive with 48% positive cells. All antibodies were stained in a Benchmark Ultra using either Ulatrview or Optiview kit. No negative controls were used for the routine stainings. The immunohistochemical stainings considered relevant for the final diagnostic workup are shown in Fig. 1 (stainings for the other markers not shown). The most common staining pattern of MCC is Chromogranin A and CK20 positivity, and TTF-1 negativity. Since the results from our immunohistochemical staining did not follow the typical pattern (and only metastases, but no primary tumor was found), the MCC diagnosis was considered, but not fully clarified at this stage. Further investigation with MCPyV PCR was performed, amplifying the small T and viral protein 1 regions with primers and probes described in Table I. 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 titers 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/m^2 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

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	GTCTCGCCAGCATTGTAGTCT
Reverse primer of small T region	MCPyV-4890.R	AAACTTTCCCAAGTAGGAGGAA
Probe of small T region	MCPyV STp	GCTATCAGTGCTTTATTCTTTGG
Forward primer of viral protein 1 region	MCPyV-1682.F	AGGCCTAGTTTTAGATTACCAGAC
Reverse primer of viral protein 1 region	MCPyV-1780.R	CTTGTGGATCTAGGCCCTGAT
Probe of viral protein 1 region	MCPyV VP1p	ACAAATGGTGGGCCTATTAC

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

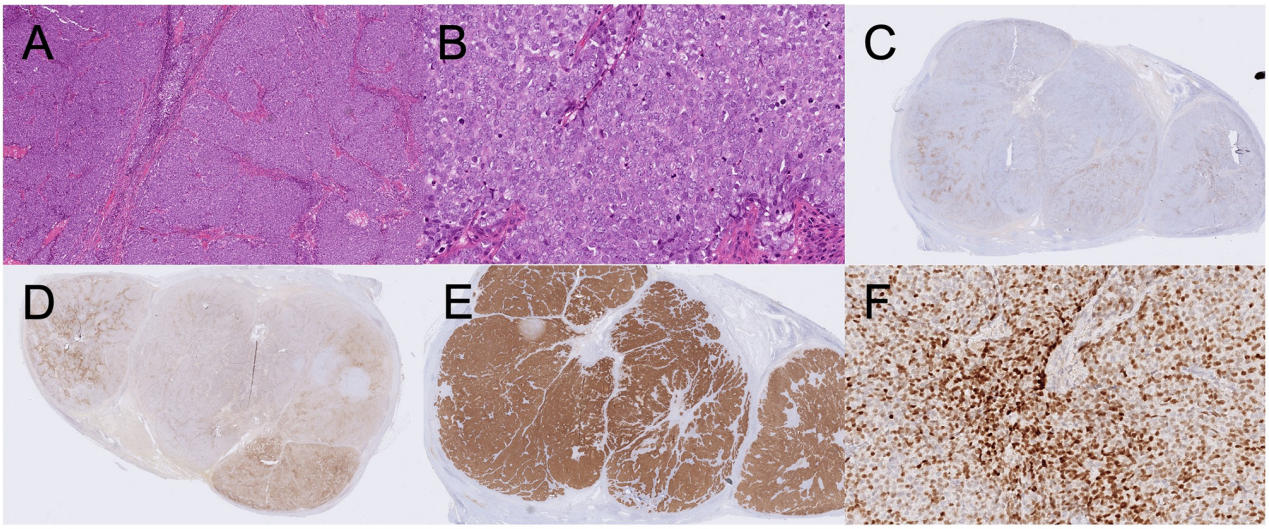

Figure 1. Immunohistochemistry from the node in the groin. (A) Routine staining with hematoxylin-eosin (20x magnification) and (B) routine staining with hematoxylin-eosin at higher magnification (40x magnification) from the node in the groin. (C) The node was considered negative for chromogranin A (10x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

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 h 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

with CT thorax/abdomen are from now on to be performed every 4-6 months.

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).

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.

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),

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.

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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.

References

1. Hoefler H, Kerl H, Rauch HJ and Denk H: New immunocytochemical observations with diagnostic significance in cutaneous neuroendocrine carcinoma. Am J Dermatopathol 6: 525-530, 1984.
2. Walsh NM: Primary neuroendocrine (Merkel cell) carcinoma of the skin: Morphologic diversity and implications thereof. Hum Pathol 32: 680-689, 2001.
3. Becker JC, Stang A, DeCaprio JA, Cerroni L, Lebbe C, Veness M and Nghiem P: Merkel cell carcinoma. Nat Rev Dis Primers 3: 17077, 2017.
4. Pavolucci L, Giannini G, Giannoccaro MP, Foschini MP, Lang B, Avoni P, Tinuper P, Vincent A and Liguori R: Paraneoplastic cerebellar degeneration and lambert-eaton myasthenia in a patient with merkel cell carcinoma and voltage-gated calcium channel antibodies. Muscle Nerve 56: 998-1000, 2017.
5. Eggers SD, Salomao DR, Dinapoli RP and Vernino S: Paraneoplastic and metastatic neurologic complications of Merkel cell carcinoma. Mayo Clin Proc 76: 327-330, 2001.
6. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, Shih KC, Lebbé C, Linette GP, Milella M, *et al*: Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: A multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 17: 1374-1385, 2016.
7. Collins JM and Gulley JL: Product review: Avelumab, an anti-PD-L1 antibody. Hum Vaccin Immunother 15: 891-908, 2019.

8. Kesner VG, Oh SJ, Dimachkie MM and Barohn RJ: Lambert-eaton myasthenic syndrome. Neurol Clin 36: 379-394, 2018.
9. O'Neill JH, Murray NM and Newsom-Davis J: The lambert-eaton myasthenic syndrome. A review of 50 cases. Brain 111: 577-596, 1988.
10. Skeie GO, Apostolski S, Evoli A, Gilhus NE, Illa I, Harms L, Hilton-Jones D, Melms A, Verschuuren J, Horge HW, *et al*: Guidelines for treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol 17: 893-902, 2010.
11. Gustafsson B, Priftakis P, Rubin J, Giraud G, Ramqvist T and Dalianis T: Human polyomaviruses were not detected in cerebrospinal fluid of patients with neurological complications after hematopoietic stem cell transplantation. Future Virol 8: 809-814, 2013.
12. Llombart B, Monteagudo C, Lopez-Guerrero JA, Carda C, Jorda E, Sanmartin O, Almenar S, Molina I, Martín JM and Llombart-Bosch A: Clinicopathological and immunohistochemical analysis of 20 cases of Merkel cell carcinoma in search of prognostic markers. Histopathology 46: 622-634, 2005.
13. Kervarrec T, Zaragoza J, Gaboriaud P, Le Gouge A, Beby-Defaux A, Le Corre Y, Hainaut-Wierzbicka E, Aubin F, Bens G, Michenet P, *et al*: Differentiating Merkel cell carcinoma of lymph nodes without a detectable primary skin tumor from other metastatic neuroendocrine carcinomas: The ELECTHIP criteria. J Am Acad Dermatol 78: 964-972 e3, 2018.
14. Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, Sedlackova E, Toumpanakis C, Anlauf M, Cwikla JB, *et al*: ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. Neuroendocrinology 103: 186-194, 2016.
15. Kuwamoto S: Recent advances in the biology of Merkel cell carcinoma. Hum Pathol 42: 1063-1077, 2011.
16. Feng H, Shuda M, Chang Y and Moore PS: Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 319: 1096-1100, 2008.
17. Sihto H, Kukko H, Koljonen V, Sankila R, Bohling T and Joensuu H: Clinical factors associated with Merkel cell polyomavirus infection in Merkel cell carcinoma. J Natl Cancer Inst 101: 938-945, 2009.
18. Duncavage EJ, Le BM, Wang D and Pfeifer JD: Merkel cell polyomavirus: A specific marker for Merkel cell carcinoma in histologically similar tumors. Am J Surg Pathol 33: 1771-1777, 2009.
19. Ordonez NG: Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. Am J Surg Pathol 24: 1217-1223, 2000.
20. Taralli S, Sollini M, Milella M, Perotti G, Filice A, Menga M, Versari A and Rufini V: (18)F-FDG and (68)Ga-somatostatin analogs PET/CT in patients with Merkel cell carcinoma: A comparison study. EJNMMI Res 8: 64, 2018.
21. Ishida Y: PD-1: Its discovery, involvement in cancer immunotherapy, and beyond. Cells 9: 1376, 2020.
22. Desch L and Kunstfeld R: Merkel cell carcinoma: Chemotherapy and emerging new therapeutic options. J Skin Cancer 2013: 327150, 2013.
23. Dohrn MF, Schone U, Kuppers C, Christen D, Schulz JB, Gess B and Tauber S: Immunoglobulins to mitigate paraneoplastic lambert eaton myasthenic syndrome under checkpoint inhibition in Merkel cell carcinoma. Neurol Res Pract 2: 52, 2020.
24. Agostini A, Merli M, Avallone G, Burzi L, Mastorino L, Parisi M, Bertuzzo D, Ferrero B, Cerrato M, Badellino S, *et al*: Lambert-eaton myasthenic syndrome and paraneoplastic cerebellar degeneration associated with merkel cell carcinoma with unknown primary: A case report. Acta Derm Venereol 101: adv00452, 2021.
25. Nguyen ND, Simmons DB, Bersabe AR, Duginski TM, Sladky JH, Walton D, Will M and Renshaw JS: Lambert-Eaton myasthenic syndrome and merkel cell carcinoma. Cutis 103: E19-E23, 2019.
26. Iyer JG, Parvathaneni K, Bhatia S, Tarabadkar ES, Blom A, Doumani R, McKenzie J, Asgari MM and Nghiem P: Paraneoplastic syndromes (PNS) associated with Merkel cell carcinoma (MCC): A case series of 8 patients highlighting different clinical manifestations. J Am Acad Dermatol 75: 541-547, 2016.
27. Bombelli F, Lispi L, Calabro F, Corsi FM and Petrucci A: Lambert-Eaton myasthenic syndrome associated to Merkel cell carcinoma: Report of a case. Neurol Sci 36: 1491-1492, 2015.
28. Lee JH, Baek SK, Han JJ, Kim HJ, Lee YA, Yoo D and Maeng CH: Lambert-Eaton myasthenic syndrome (LEMS) in a patient with lung cancer under treatment with pembrolizumab: A case study. J Chemother 13: 1-6, 2022.
29. Sakaguchi T, Kokubo Y, Furuhashi K, Nakamura Y, Suzuki Y, Ito K, Fujiwara K, Nishii Y, Taguchi O and Hataji O: An extensive-stage small-cell lung cancer case with preexisting lambert-eaton myasthenic syndrome successfully treated with an immune checkpoint inhibitor. Clin Lung Cancer 23: e273-e275, 2022.
30. Gill AJ, Gandhy S and Lancaster E: Nivolumab-associated lambert-eaton myasthenic syndrome and cerebellar dysfunction in a patient with a neuroendocrine tumor. Muscle Nerve 63: E18-E21, 2021.
31. Kunii E, Owaki S, Yamada K, Yoshihara M, Yamaba Y, Takakuwa O, Toyoda T and Akita K: Lambert-eaton myasthenic syndrome caused by atezolizumab in a patient with small-cell lung cancer. Intern Med 61: 1739-1742, 2022.
32. Nakatani Y, Tanaka N, Enami T, Minami S, Okazaki T and Komuta K: Lambert-eaton myasthenic syndrome caused by nivolumab in a patient with squamous cell lung cancer. Case Rep Neurol 10: 346-352, 2018.