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Paraneoplastic syndromes associated with Merkel cell carcinoma: A case series of eight patients highlighting different clinical manifestations

Jayasri Iyer, MD[1], **Kaushik Parvathaneni**[1], **Shailender Bhatia, MD**[2], **Erica Shantha, MD**[1], **Astrid Blom, MD**[1], **Ryan Doumani, BS**[1], **Jill McKenzie, MD**[1], **Maryam M. Asgari, MD, MPH**[3,4], and **Paul Nghiem, MD, PhD**[1]

[1]Department of Medicine, Dermatology Division, University of Washington, Seattle, Washington, USA

[2]Department of Medicine, Medical Oncology Division, University of Washington, Seattle, WA

[3]Division of Research, Kaiser Permanente Northern California, Oakland, California, USA

[4]Department of Dermatology, Massachusetts General Hospital, Boston, MA, USA

Abstract

Background—Paraneoplastic syndromes are commonly associated with neuroendocrine cancers, such as small cell lung cancer.

Objectives—We examined the association of paraneoplastic syndromes in Merkel cell carcinoma (MCC), a rare neuroendocrine skin cancer.

Methods—We identified paraneoplastic syndromes associated with MCC based on chart review of a Seattle-based repository and also examined the incidence of MCC-associated hyponatremia in an independent cohort within Kaiser Permanente Northern California (KPNC).

Results—Eight paraneoplastic syndrome (PNS) cases were identified from the Seattle repository. Three distinct PNS types were observed: cerebellar degeneration (one case), Lambert-Eaton myasthenic syndrome (two cases), and malignancy-associated hyponatremia (five cases). Moreover, the incidence of severe hyponatremia (serum sodium <125 mmol/L) coincident with MCC was identified among 4.3% (9 of 211) MCC patients in the KPNC cohort.

Limitations—We did not have access to complete medical records on all patients so it was not possible to determine the prevalence of paraneoplastic syndromes in MCC.

Corresponding author: Paul Nghiem, MD, PhD, 850 Republican Street, Seattle, WA 98109, Phone: 206-221-2632; Fax: 206-221-4364, pnghiem@uw.edu.

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Conclusions—MCC can be associated with paraneoplastic syndromes similar to those found in other neuroendocrine cancers. Clinicians should be aware of these presentations as paraneoplastic syndromes often precede the identification of the underlying malignancy and usually resolve with appropriate treatment of the cancer.

Keywords

Merkel cell carcinoma; paraneoplastic syndrome; Lambert-Eaton myasthenic syndrome; cerebellar degeneration; malignancy-associated hyponatremia; neuroendocrine

Background

A paraneoplastic syndrome (PNS) is a physiological response to an underlying malignancy caused by ectopic hormone secretion or an autoimmune response to cancer-associated antigens.[1] Paraneoplastic syndromes have been reported in association with several cancers, most commonly small cell lung cancer (SCLC), breast, gynecologic, and hematologic malignancies.[2,3] PNS types and their presentations differ based on the underlying malignancy. Neuroendocrine malignancies (bronchial carcinoids, carcinoid tumors, and pancreatic islet cell tumors) are associated with a variety of PNS types including Cushing's syndrome, acromegaly, and hypercalcemia.[4]

While it is estimated that up to 8% of cancers are associated with paraneoplastic syndromes,[2] the prevalence in patients with SCLC is up to 20%.[1] SCLC is reported to be associated with Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) and Lambert-Eaton myasthenic syndrome (LEMS).[5,6] SCLC is a neuroendocrine tumor with similar histological features to Merkel cell carcinoma (MCC), an uncommon but often aggressive cutaneous neuroendocrine cancer. MCC is associated with sun exposure, advanced age, fair skin, immune suppression, and the Merkel cell polyomavirus (MCPyV), identified in 80–90% MCCs.[7] Given a shared neuroendocrine differentiation with SCLC, it is likely that MCC may demonstrate similar presentations of paraneoplastic syndromes.

The literature regarding paraneoplastic syndromes in MCC is limited to individual case reports (summarized in Table 1). Here we describe eight new cases of paraneoplastic syndromes associated with MCC. The incidence of severe MCC-associated hyponatremia is also explored in an independent cohort.

Methods

Patients

The cases analyzed were from the Repository of Data and Specimens for MCC at the University of Washington in Seattle (n=452) and Kaiser Permanente Northern California (KPNC) (n= 211), a large, integrated healthcare delivery system. This study was IRB-approved by Fred Hutchinson Cancer Research Center (IRB# 6585) and KPNC (IRB #CN-09Masgar-03). Patients were diagnosed with MCC between 1980 and 2014. Analyses for this study were carried out between August 2006 and January 2014.

Identification of paraneoplastic syndrome cases

Patients in the Seattle based repository were followed prospectively for survival and recurrence. Although no formal protocol or screening was used to detect paraneoplastic syndromes across all patients in the cohort, those with symptoms suggestive of PNS were evaluated in detail for evidence of a paraneoplastic syndrome based on the previously described characteristics of PNS in MCC and other neuroendocrine carcinomas. Cases were reviewed using established criteria to confirm the diagnosis of LEMS and paraneoplastic cerebellar degeneration.[8,9]

Severe hyponatremia was defined as one serum sodium value below 125mmol/L.[10] Access to medication history was available for patients in the Seattle repository and were reviewed to ensure that no patient was taking medications known to induce hyponatremia. To classify a patient as having malignancy-associated hyponatremia, there must have been clinically significant MCC at time of severe hyponatremia and resolution of hyponatremia upon successful MCC treatment.

To examine the incidence of severe hyponatremia among an independent cohort of MCC cases, serum sodium values from 211 patients in the KPNC repository were reviewed. The median number of serum sodium samples available per patient was 14 (range: 1–106). To be classified as severe hyponatremia, patients needed to have: 1) serum sodium <125 mmol/L, 2) evidence of MCC at time of hyponatremia, and, 3) no prior history of hyper- or hyponatremia. Five cases were excluded as they did not meet these criteria. Additionally, we verified that the KPNC patients were not receiving chemotherapeutic drugs at the time of their low serum sodium, as chemotherapy can lead to hyponatremia.[11] However, because not all potentially relevant treatment and medication records were accessible at the time of analysis of the KPNC cohort, these cases were identified as severe hyponatremia coincident with MCC but not conclusively determined to be paraneoplastic in nature.

Results

Paraneoplastic syndromes were identified in eight MCC patients within the Seattle repository: one patient had paraneoplastic cerebellar degeneration with autonomic neuropathy, two patients had LEMS, and five patients had malignancy-associated hyponatremia. The clinical characteristics of these reported cases are summarized in Table II. Seven patients were male and one was female. The median age at diagnosis of MCC was 58 years (range: 52–83 years) and median age at presentation of paraneoplastic syndrome was 58 years (range: 54–82 years).

All paraneoplastic syndromes in the present study were associated with advanced MCC (regional nodal or distant metastatic). Of the eight patients that were classified as having a PNS, three died of MCC and five were alive at the end of the study period. Three of the five patients who were alive had no evidence of disease for a median of five years (range: 5–7 years). Two of the three living patients without evidence of disease had an autoimmune paraneoplastic syndrome that presented prior to their MCC diagnosis. The median follow up time for all patients was 38 months (range: 9–86 months).

Among the 211 KPNC cases, nine patients (4.3%) had severe hyponatremia that met criteria for being MCC-associated (see Methods). Serum sodium levels ranged from 110–124 mmol/L and the median number of sodium values below 125 mmol/L per patient was four (range 1–18). In all KPNC cases, severe hyponatremia was associated with nodal or distant metastatic MCC. Eight of these nine patients died of MCC and one died of a non-MCC cause. Median interval from time of developing hyponatremia to death among these patients was 14 days (range: 3–143 days).

Case Reports

The following cases illustrate how three specific paraneoplastic syndromes can manifest in MCC patients and provide details that could be helpful in their recognition and management.

Cerebellar Degeneration with Autonomic Neuropathy

A 63-year-old man had sudden onset of gait instability with significant difficulty in coordinating movements, swallowing, and moderate slurring of speech in July 2006. Magnetic resonance imaging (MRI) suggested focal inflammation of the cerebellum and brainstem based on increased fluid attenuated inversion recovery (FLAIR) signal. A few months later, excisional biopsy of an enlarged right iliofemoral lymph node revealed MCC without a known primary lesion. The patient underwent completion lymphadenectomy and received adjuvant radiation therapy (RT) to the right inguinal and pelvic nodes. Five months after radiation therapy was completed, a follow-up brain MRI showed resolution of the previously noted FLAIR abnormality and by one year after MCC therapy, the patient's neurological symptoms had improved. Resolution of these symptoms following therapy is consistent with autoimmune paraneoplastic cerebellar degeneration. Of note, this patient did not have detectable anti-neuronal antibodies which are often, but not always, associated with this paraneoplastic syndrome.[8,12] Seven years after his initial diagnosis, he has no evidence of disease and minimal neurological symptoms.

Lambert-Eaton myasthenic syndrome

A 58-year-old man developed tingling in his hands, legs, and face in February 2009. Neurologic evaluation was negative including nerve conduction studies and an MRI. The tingling sensation rapidly worsened in November 2009 with development of proximal muscle weakness and loss of motor strength. Antinuclear antibodies (ANA) that had initially been negative became positive in early 2010 (1:640; atypical speckled pattern) and a CT scan showed no evidence of malignancy. A few months later, the patient noted a "lump" in his right axilla. A biopsy of this 3.8 centimeter mass revealed nodal MCC without a known primary lesion and he underwent right axillary lymph node dissection. Antibodies against voltage-gated calcium channels revealed a titer of >23,000 pM/L (normal: <50 pM/L[13]), consistent with Lambert-Eaton myasthenic syndrome (LEMS). Antibody titers were conclusive in this case, although 15% of LEMS cases do not involve antibodies to voltage gated calcium channels.[14] Following adjuvant RT, this patient regained strength. Five years after initial MCC diagnosis, he has no evidence of disease or symptoms of LEMS.

Malignancy-associated hyponatremia

A 56-year-old man presented in June 2008 with chronic fatigue and a new mass in his right groin that had been enlarging for over a year. One month later he developed severe hyponatremia with a serum sodium level of 119 mmol/L (normal: 135–145 mmol/L[15]). Ultrasound revealed a five centimeter mass in the right lower abdomen that was excised and found to be nodal MCC without a known primary lesion. Serum sodium levels normalized within 20 days of excision of MCC. The development of hyponatremia and its resolution after resection of the tumor suggests these symptoms were paraneoplastic in nature. Clinical exam along with plasma osmolality, urine osmolality, and urine sodium evaluation between July 2008 and December 2008 met established essential diagnostic criteria for SIADH.[1516] Five years after initial diagnosis, he has no evidence of MCC or hyponatremia.

Discussion

Timely identification of a paraneoplastic syndrome can serve as an important sign of an underlying malignancy. Three of the eight cases identified in this report presented with a PNS prior to their MCC diagnosis, thereby prompting work up and discovery of the occult malignancy. Additionally, one case presented with symptoms of a PNS prior to detection of metastatic disease. The types of paraneoplastic syndrome identified with MCC have been described in other neuroendocrine malignancies: cerebellar degeneration (one case), Lambert-Eaton myasthenic syndrome (two cases), and malignancy-associated hyponatremia (five cases). In addition, among 211 cases from KPNC with detailed serum sodium data, nine patients (4.3%) had new onset severe hyponatremia coincident with advanced MCC.

Previously, the association of a PNS with MCC has been reported in 13 individual case reports. Notably, 10 of the 13 cases were autoimmune neurologic paraneoplastic syndromes including LEMS, paraneoplastic cerebellar degeneration, and paraneoplastic encephalomyelitis. In this report, malignancy-associated hyponatremia in MCC was identified more frequently than among MCC-PNS cases previously reported in the literature. This may be a reflection of biases in both detection and reporting. Specifically, as compared to SCLC patients, for which there is a well-known association with SIADH, MCC patients may not often be assessed for serum sodium abnormalities, unless patients are symptomatic. Also, as the association is less established than an autoimmune neurologic PNS, it may be less likely to be reported.

The manifestations of paraneoplastic syndromes in MCC reported here are similar to those in small cell lung cancer (SCLC), including LEMS and malignancy-associated hyponatremia. Among SCLC-associated paraneoplastic syndromes, SIADH and LEMS are more commonly observed. Approximately 11% of SCLC patients develop SIADH and 3% develop LEMS.[5,17] Because not all records were available on all patients, it was not possible to determine the prevalence of PNS in MCC. However, it appears likely that it is lower than the approximately 20% reported in SCLC.[1]

Interestingly, some reports suggest that there may be an association in SCLC between improved prognosis and auto-immune PNS. In SCLC, ectopic hormone production (such as adrenocorticotropic hormone or anti-diuretic hormone) has been associated with advanced

disease stage and poor prognosis.[1,18,19] However, antibody-mediated paraneoplastic syndromes, particularly LEMS, have been associated with more favorable outcomes in SCLC.[20] In our cohort, because the sample size was small, we were unable to determine if this was the case. Nevertheless, two of the three patients with autoimmune PNS were alive with no evidence of MCC at the conclusion of this study, despite having regional nodal metastatic disease at presentation. In contrast, of the five patients with malignancy-associated hyponatremia, only one was alive with no disease, two were alive with disease, and two had died of MCC.

As paraneoplastic syndromes are due to the presence of tumor cells in the body, treatment of the underlying malignancy typically leads to resolution of the PNS. The PNS cases in this report largely reflect this concept; in four cases, successful treatment was followed by resolution of paraneoplastic symptoms. One of these patients, who had malignancy-associated hyponatremia, subsequently developed progressive MCC and died, but did not develop a relapse of the malignancy-associated hyponatremia. In the remaining four cases, treatment of MCC was not effective and paraneoplastic syndromes persisted. Three of these four patients died of MCC within the study period.

This study has several limitations. Complete chart review on all MCC patients in the Seattle based repository was not feasible and was limited to those with suspicious PNS-like symptoms who were then evaluated in detail. Because a formal screen for PNS was not prospectively carried out on all cases, the prevalence of paraneoplastic syndromes among MCC patients could not be determined. In the KPNC cohort, certain clinical data such as medication history and urine electrolytes were not ascertained. Therefore, we could not determine the etiology of hyponatremia or verify that it resolved with appropriate MCC treatment. Consequently, we did not classify these nine KPNC cases of severe MCC-hyponatremia as definitively paraneoplastic in nature. These KPNC cases nonetheless support the observation that hyponatremia is associated with MCC.

Paraneoplastic syndromes associated with MCC follow a similar pattern to those associated with SCLC, including malignancy-associated hyponatremia, paraneoplastic cerebellar degeneration, and LEMS. Although we do not believe that formal screening for PNS in MCC is indicated as these presentations are uncommon, we highlight these associations because we have observed delayed recognition of PNS in MCC because of the scarcity of their description in the literature. Specifically, unexplained neurological changes and or hyponatremia should raise suspicions of a possible link to a PNS etiology. This report aims to augment awareness of the occurrence and nature of paraneoplastic syndromes that may be associated with MCC, and contribute to improved detection and management of MCC and associated paraneoplastic syndromes.

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Abbreviations and Acronym list

MCC	Merkel cell carcinoma
KPNC	Kaiser Permanente Northern California
PNS	Paraneoplastic syndrome
SCLC	Small cell lung cancer
SIADH	Syndrome of Inappropriate Anti-Diuretic Hormone
LEMS	Lambert-Eaton myasthenic syndrome
MCPyV	Merkel cell polyomavirus
MRI	Magnetic resonance imaging
FLAIR	Fluid attenuated inversion recovery
CT	Computed tomography
RT	Radiation therapy
ANA	Antinuclear antibodies
NA	Not available
UP	Unknown primary
Y	Yes
N	No

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Table I

Reports of MCC-associated paraneoplastic syndromes in the literature

Author[citation]	Age/sex	Symptoms
Balegno et al.[21]	NA *	Cerebellar degeneration
Batchelor et al.[22]	75/F	Encephalomyelitis with ataxia
Blondin et al.[23]	46/F	Hyponatremia, memory impairment, seizures, (Hyponatremia-associated malignancy/SIADH)
Bombelli et al.[24]	67/M	Weakness, dry hands and feet, diminished tendon reflexes (Lambert-Eaton myasthenic syndrome)
Cher et al.[25]	NA *	Paraneoplastic brainstem encephalitis
Donovan et al.[26]	NA *	Parathyroid hormone-related protein mediated hypercalcemia
Eggers et al.[27]	69/M	Extremity weakness, unsteady gait, fatigue while walking (Lambert-Eaton myasthenic syndrome)
Greenlee et al.[28]	77/F	Paresthesias, nausea, disequilibrium, facial palsy, extremity paresis, constipation, vertical nystagmus (paraneoplastic neurological disease)
Hocar et al.[29]	58/F	Necrotizing myopathy
Lopez et al.[30]	46/F	Extremity weakness, fatigue when walking (paraneoplastic neurological disease)
Siau, et al.[31]	70/F	Lower limb weakness, dyspnea, myopathic gait (Lambert Eaton myasthenic syndrome)
Voulgari, et al.[32]	84/F	Swelling of right hip, right knee, bilateral heels (paraneoplastic polyarthritis)
Zhang, et al.[33]	50/M	Paraneoplastic cerebellar degeneration

* NA = Not available

Table II

Characteristics of patients with paraneoplastic syndromes associated with MCC

PNS type	Sex	Age at MCC diagnosis	Stage at MCC diagnosis	Age at PNS diagnosis	Extent of disease at PNS diagnosis	Resolution of PNS?	Vital Stats (at end of study period)	Follow up time (Months)
Hyponatremia	M	52	IIA	53	Distant metastatic disease	Y- following palliative radiation therapy	Alive with disease	47
Hyponatremia	F	54	IV	55	Distant metastatic disease	N – disease progression resistant to multiple therapies	Died of disease	18
Hyponatremia	M	66	IIA	69	Distant metastatic disease	N –recurrent hyponatremia following palliative radiation therapy and progressive disease	Died of Disease	32
Hyponatremia	M	52	IIIB - UP **	54	Distant metastatic disease	N – disease progression resistant to chemotherapy	Alive with Disease	20
Hyponatremia	M	57	IIIB - UP **	56	Onset of PNS prompted scan, occult disease detected	Y – after lymph node dissection	Alive with no disease	62
*LEMS	M	59	IIIB – UP **	59	Onset of PNS prompted work up, occult disease detected after persistent symptoms and scans	Y – after lymph node dissection and RT to tumor	Alive with no disease	44
*LEMS	M	82	IIB	82	Presented with symptoms of PNS prior to detection of distant metastatic disease	N – disease progression resistant to chemotherapy	Died of Disease	9
Cerebellar Degeneration	M	63	IIIB – UP **	63	Onset of PNS prompted scan, occult disease detected	Y - Improvement of neurological symptoms after completion lymphadenectomy and radiation therapy	Alive with no disease	86

* LEMS = Lambert-Eaton Myasthenic Syndrome

** UP = Unknown primary